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Fremanezumab for the Preventive Treatment of Chronic Migraine

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ABSTRACT

BACKGROUND

Fremanezumab, a humanized monoclonal antibody targeting calcitonin gene–related peptide (CGRP), is being investigated as a preventive treatment for migraine. We compared two fremanezumab dose regimens with placebo for the prevention of chronic migraine.

METHODS

In this phase 3 trial, we randomly assigned patients with chronic migraine (defined as headache of any duration or severity on ≥15 days per month and migraine on ≥8 days per month) in a 1:1:1 ratio to receive fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8), or matching placebo. Both fremanezumab and placebo were administered by means of subcutaneous injection. The primary end point was the mean change from baseline in the average number of headache days (defined as days in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least a moderate level or days in which acute migraine–specific medication [triptans or ergots] was used to treat a headache of any severity or duration) per month during the 12 weeks after the first dose.

RESULTS

Of 1130 patients enrolled, 376 were randomly assigned to fremanezumab quarterly, 379 to fremanezumab monthly, and 375 to placebo. The mean number of baseline headache days (as defined above) per month was 13.2, 12.8, and 13.3, respectively. The least-squares mean (±SE) reduction in the average number of headache days per month was 4.3±0.3 with fremanezumab quarterly, 4.6±0.3 with fremanezumab monthly, and 2.5±0.3 with placebo (P<0.001 for both comparisons with placebo). The percentage of patients with a reduction of at least 50% in the average number of headache days per month was 38% in the fremanezumab-quarterly group, 41% in the fremanezumab-monthly group, and 18% in the placebo group (P<0.001 for both comparisons with placebo). Abnormalities of hepatic function occurred in 5 patients in each fremanezumab group (1%) and 3 patients in the placebo group (<1%).

CONCLUSIONS

Fremanezumab as a preventive treatment for chronic migraine resulted in a lower frequency of headache than placebo in this 12-week trial. Injection-site reactions to the drug were common. The long-term durability and safety of fremanezumab require further study. (Funded by Teva Pharmaceuticals; ClinicalTrials.gov number, NCT02621931.)

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Migraine is a complex neurologic disorder that is characterized primarily by recurrent attacks of pulsating headache pain of at least moderate severity.[1,2] It has a global prevalence of 15 to 18% and is a leading cause of disability worldwide.[3] Chronic migraine, occurring in approximately 2% of the population, has been defined as the occurrence of at least 15 days with headache per month for at least 3 months.[2,4] With daily or near-daily attacks, persons with chronic migraine have functional impairment and a lower quality of life than those with less-frequent migraine.[4] Expert opinion has been that patients with chronic migraine should receive preventive treatment[2,5,6]; however, these treatments may be underused, not adhered to, associated with side effects, or ineffective.[7,8]

Fremanezumab (TEV-48125) is a humanized IgG2a monoclonal antibody that selectively and potently binds to calcitonin gene–related peptide (CGRP),[9,10] a 37–amino acid neuropeptide involved in central and peripheral pathophysiological events of migraine.[11-13] Fremanezumab targets both α and β isoforms of the CGRP ligand (not the receptor), has flexible dosing, and is administered by means of subcutaneous injection.[9,10] In a phase 2 trial involving patients with chronic migraine, the numbers of migraine days and headache days were significantly lower with fremanezumab than with placebo, and no serious treatment-related adverse events occurred.[14] We conducted a 16-week, double-blind, randomized, placebo-controlled, phase 3 trial with a 12-week active-intervention phase to evaluate the efficacy, safety, and side-effect profile of two subcutaneous dose regimens of fremanezumab for the preventive treatment of chronic migraine.

Methods

Trial Oversight

The protocol, available with the full text of this article at NEJM.org, was approved by relevant ethics committees and institutional review boards. The authors vouch for the conduct of the trial, adherence to the protocol, and the accuracy and completeness of the data and analyses and the reporting of adverse events. The trial complied with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and relevant national and local regulations. At the time of screening, participants signed consent forms for both this trial and a concurrent trial of fremanezumab for episodic migraine (ClinicalTrials.gov number, NCT02629861). The trial sponsor, Teva Pharmaceuticals, provided the trial medication, performed the data analysis, and funded the trial. Assistance with manuscript preparation was provided by a medical writer funded by the sponsor.

Trial Participants

Patients were recruited at 132 sites in nine countries from March 2016 through January 2017. These sites were clinics caring for persons with headaches, and potential participants were identified from their databases. Key inclusion criteria were an age of 18 to 70 years, a history of migraine (according to the criteria of the International Classification of Headache Disorders, 3rd edition [beta version], or ICHD-3 beta) for at least 12 months, and the fulfillment of the criteria for chronic migraine during the 28-day preintervention period (headache of any duration or severity on ≥15 days and headache meeting ICHD-3 beta criteria for migraine on ≥8 days). The protocol allowed inclusion of up to 30% of patients using a stable dose of one migraine-preventive medication (hereafter referred to as preventive medication) for at least 2 months before the beginning of the preintervention period to continue these medications.

Key exclusion criteria were the use of onabotulinumtoxinA during the 4 months before screening; the use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during the 2 months before screening; the use of opioid or barbiturate medications on more than 4 days during the preintervention period; and a lack of efficacy, after an adequate therapeutic trial, of at least two of four clusters of preventive medications, the details of which are provided in the protocol.

Trial Design

This randomized, double-blind, placebo-controlled, parallel-group trial consisted of a screening visit, a 28-day preintervention period, and a 12-week intervention period, with a final evaluation at week 12. On the basis of the screening visit and information collected in a daily diary during the preintervention period, patients were enrolled in the appropriate trial or were excluded if they were not eligible for either trial.

Eligible patients were randomly assigned in a 1:1:1 ratio to receive fremanezumab quarterly, fremanezumab monthly, or placebo. All the patients received three abdominal subcutaneous injections at baseline and one injection at weeks 4 and 8. In the fremanezumab-quarterly group, patients received a single dose of 675 mg of fremanezumab at baseline (three injections of 225 mg per 1.5 ml), followed at weeks 4 and 8 by placebo (one 1.5-ml injection). In the fremanezumab-monthly group, patients received 675 mg of fremanezumab at baseline (as above) and 225 mg of fremanezumab at weeks 4 and 8 (one injection of 225 mg per 1.5 ml). In the placebo group, placebo was administered as three 1.5-ml injections at baseline and one 1.5-ml injection at weeks 4 and 8. Randomization was performed by means of electronic interactive-response technology, with stratification according to sex, country, and baseline use of preventive medication (yes or no). Patients, investigators, the sponsor, and trial staff were unaware of the trial-group assignments.

Patients were seen at five scheduled visits for protocol-specified evaluations: at screening, baseline, weeks 4 and 8, and week 12, or at the time of early withdrawal from the trial. Patients who withdrew prematurely had final protocol-specified evaluations performed as soon as possible after withdrawal. Headache data (e.g., occurrence, duration, and pain severity; occurrence of photophobia, phonophobia, nausea, or vomiting; and any use of migraine medication) were captured daily through an electronic headache-diary device (ERT DIARYpro platform on the Bluebird Pidion BM-170 device).

TRIAL END POINTS

The primary end point was the mean change in the average number of headache days (days in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least a moderate level or days in which acute migraine–specific medication [triptans or ergots] was used to treat a headache of any severity or duration) per month, comparing the baseline 28-day preintervention period with the 12-week period after the first dose of the trial regimen.

Secondary end points were the mean change from baseline in the average number of migraine days per month, the percentage of patients with a reduction of at least 50% in the average number of headache days per month, and the mean change from baseline in the average number of days per month in which acute headache medication was used during the 12-week period after the first dose. A migraine day was defined as a calendar day in which headache pain lasted at least 4 consecutive hours and met criteria for migraine (with or without aura) or probable migraine (subtype in which only one migraine criterion is absent), or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any duration. Other secondary end points included the mean change from baseline in the number of headache days during the 4-week period after the first dose in all the patients and during the 12-week period after the first dose in patients not receiving concomitant preventive medication, as well as the mean change in the score on the six-item Headache Impact Test (HIT-6; scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability)[15] from baseline (day 0) to 4 weeks after administration of the last dose of the trial regimen.

Safety and side-effect profiles were evaluated according to reported adverse events, vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate), physical examination, 12-lead electrocardiography, clinical laboratory tests (serum chemical, hematologic, coagulation, and urinalysis tests), systematic assessments of local injection-site reactions (erythema, induration, ecchymosis, and pain, all evaluated both immediately and 1 hour after dose administration), concomitant medication use, and suicidal ideation and behavior as assessed by means of scores on the electronic Columbia–Suicide Severity Rating Scale. Serum levels of antidrug antibodies were assessed with the use of a validated method.

STATISTICAL ANALYSIS

Estimations based on the phase 2b trial of fremanezumab in chronic migraine[14] predicted that a sample of 867 patients who had completed the trial and could be evaluated would provide 90% power to detect a mean (±SD) difference of 1.7±6.3 in the average number of headache days per month between the fremanezumab-monthly group and the placebo group at a two-sided alpha level of 0.05. With an anticipated rate of discontinuation of 15%, 1020 participants were planned for randomization in this trial. Efficacy

analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of a trial regimen and had at least 10 days of postbaseline efficacy assessments regarding the primary end point. Safety analyses included all randomly assigned patients who received at least one dose of a trial regimen.

The primary end point was analyzed with the use of an analysis of covariance. Trial regimen, sex, country, and baseline use of preventive medication (yes or no) were used as fixed effects, and the baseline number of migraine days and of years since the onset of migraines were covariates. We calculated 95% confidence intervals for the least-squares mean differences between each fremanezumab group and the placebo group. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from the normality assumption as assessed by means of the Shapiro–Wilk test. For management of missing data in the primary analysis, the average number of headache days per month during the 12-week period was prorated to a 28-day equivalent with the use of all postbaseline observations. The same analyses were used for relevant secondary end points. For the percentage of patients with a reduction of at least 50% in the average number of headache days per month, the Cochran–Mantel–Haenszel test was used, with baseline use of preventive medication (yes or no) as a stratification variable.

To control the type I statistical error rate at 0.05, a hierarchical testing procedure was applied, with a prespecified sequence of comparisons beginning with the primary end point and proceeding to secondary end points in the order given in the protocol. Each comparison was performed only if the preceding comparison had a two-sided P value of 0.05 or less. Results are presented in the sequence in which end points were evaluated.

RESULTS

PATIENTS

A total of 1130 patients were randomly assigned to one of the three trial regimens: 376 to fremanezumab quarterly, 379 to fremanezumab monthly, and 375 to placebo (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Baseline demographic and clinical characteristics were similar among the three groups (Table 1). The mean number of baseline headache days (as defined above) per month was 13.2 in the fremanezumab-quarterly group, 12.8 in the fremanezumab-monthly group, and 13.3 in the placebo group. Of the randomly assigned patients, 1034 completed the trial: 349 (93%) in the fremanezumab-quarterly group, 343 (91%) in the fremanezumab-monthly group, and 342 (91%) in the placebo group (Fig. S1 in the Supplementary Appendix).

EFFICACY

With respect to the primary end point, the mean (±SE) number of headache days per month was reduced by 4.3±0.3 days in the fremanezumab-quarterly group, 4.6±0.3 days in the fremanezumab-monthly group, and 2.5±0.3 days in the placebo group (P<0.001 for both comparisons with placebo) (Table 2 and Fig. 1A). For the 12 weeks of the intervention period, patients receiving placebo had an average of 10.4±6.4 headache days, as compared with 8.5±6.3 days for those receiving fremanezumab quarterly and 8.0±6.3 days for those receiving fremanezumab monthly.

There was a larger reduction in the average number of migraine days per month with fremanezumab quarterly (by 4.9±0.4 days) and fremanezumab monthly (by 5.0±0.4 days) than with placebo (by 3.2±0.4 days) (P<0.001 for both comparisons with placebo) (Table 2 and Fig. 1B). Significantly more patients who received fremanezumab had a reduction of at least 50% in the average number of headache days per month (quarterly regimen, 38%; monthly regimen, 41%) than did patients who received placebo (18%) (P<0.001 for both comparisons with placebo) (Table 2). There was a larger reduction in the average number of days per month in which acute headache medication was used in the fremanezumab groups (by 3.7±0.3 days with the quarterly regimen and by 4.2±0.3 days with the monthly regimen) than in the placebo group (by 1.9±0.3 days) (P<0.001 for both comparisons with placebo) (Table 2).

Treatment effects were observed in the average number of headache days per month during the 4-week period after the first dose for all the patients and during the 12-week period after the first dose in the subgroup of patients not receiving concomitant preventive medication (P<0.001 for all comparisons with placebo) (Table 2). The degree of headache-related disability decreased between baseline and the 4-week period after

Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population, According to Trial Group.*

Characteristic	Fremanezumab Quarterly (N=376)	Fremanezumab Monthly (N=379)	Placebo (N=375)
Age — yr	42.0±12.4	40.6±12.0	41.4±12.0
Body-mass index†	26.6±5.4	26.5±5.1	26.5±5.0
Female sex — no. (%)	331 (88)	330 (87)	330 (88)
Disease history			
Time since initial migraine diagnosis — yr	19.7±12.8	20.1±12.0	19.9±12.9
Current use of preventive medication — no. (%)	77 (20)	85 (22)	77 (21)
Current use of acute headache medication — no. (%)	359 (95)	360 (95)	358 (95)
Previous use of topiramate — no. (%)	106 (28)	117 (31)	117 (31)
Previous use of onabotulinumtoxinA — no. (%)	66 (18)	50 (13)	49 (13)
Disease characteristics during 28-day preintervention period			
Headache days‡	13.2±5.5	12.8±5.8	13.3±5.8
Days with headache of any severity and duration	20.4±3.9	20.3±4.3	20.3±4.2
Migraine days§	16.2±4.9	16.0±5.2	16.4±5.2
Days of use of any acute headache medications	13.1±6.8	13.1±7.2	13.0±6.9
Days of use of migraine-specific acute headache medications	11.3±6.2	11.1±6.0	10.7±6.3
HIT-6 score¶	64.3±4.7	64.6±4.4	64.1±4.8

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization. Patients in the fremanezumab-quarterly group received 675 mg at baseline and placebo at weeks 4 and 8; those in the fremanezumab-monthly group received 675 mg at baseline and 225 mg at weeks 4 and 8; and those in the placebo group received placebo at baseline and at weeks 4 and 8. There were no significant between-group differences at baseline for any characteristic.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ A headache day was defined as a calendar day in which headache pain lasted at least 4 consecutive hours and had a peak severity of at least a moderate level, or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any severity or duration.

§ A migraine day was defined as a calendar day in which headache pain lasted at least 4 consecutive hours and met criteria for migraine (with or without aura) or probable migraine (subtype in which only one migraine criterion is absent), or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any duration.

¶ The six-item Headache Impact Test (HIT-6) questionnaire assesses headache-related disability over the preceding 4 weeks, with scores ranging from 36 to 78 and with higher scores reflecting greater disability.

the last dose, with significantly greater reductions in HIT-6 scores with fremanezumab quarterly (by 6.4±0.5 points) and fremanezumab monthly (by 6.8±0.4 points) than with placebo (by 4.5±0.5 points) (P<0.001 for both comparisons with placebo) (Table 2).

SAFETY

Adverse events were reported for 64% of the patients receiving placebo, 70% of those receiving fremanezumab quarterly (P=0.06 vs. placebo), and 71% of those receiving fremanezumab monthly (P=0.03 vs. placebo) (Table 3). Events were mild to moderate in severity in 95 to 96% of the patients in the three groups. A total of 20 patients discontinued the trial owing to adverse events, including 1% in the fremanezumab-quarterly group, 2% in the fremanezumab-monthly group, and 2% in the placebo group.

Injection-site reactions were reported in 40% of the patients receiving placebo, 47% of those receiving fremanezumab quarterly (P=0.08 vs. placebo), and 47% of those receiving fremanezumab monthly (P=0.03 vs. placebo); the severity of injection-site reactions did not differ significantly among the trial groups. The most common adverse event was injection-site pain, which occurred in 30% of the patients in the fremanezumab-quarterly group, 26% of those in the fremanezumab-monthly group, and 28% of those in the placebo

Table 2. Primary and Secondary End Points in the Modified Intention-to-Treat Population.*

End Point	Fremanezumab Quarterly (N=375)†	Fremanezumab Monthly (N=375)†	Placebo (N=371)
Primary end point			
Average no. of headache days per month			
Mean value during 12-wk period after first dose	8.5±6.3	8.0±6.3	10.4±6.4
Least-squares mean change from baseline during 12-wk period after first dose	−4.3±0.3	−4.6±0.3	−2.5±0.3
Difference vs. placebo	−1.8±0.3	−2.1±0.3	—
Secondary end points			
Average no. of migraine days per month			
Least-squares mean change from baseline during 12-wk period after first dose	−4.9±0.4	−5.0±0.4	−3.2±0.4
Difference vs. placebo	−1.7±0.4	−1.8±0.4	—
≥50% Reduction in average no. of headache days per month — no. of patients (%)	141 (38)	153 (41)	67 (18)
Average no. of days of use of any acute headache medication per month			
Least-squares mean change from baseline during 12-wk period after first dose	−3.7±0.3	−4.2±0.3	−1.9±0.3
Difference vs. placebo	−1.8±0.3	−2.3±0.3	—
Average no. of headache days per month			
Least-squares mean change from baseline during 4-wk period after first dose	−4.4±0.3	−4.5±0.3	−2.1±0.3
Difference vs. placebo	−2.3±0.4	−2.4±0.4	—
Average no. of headache days per month in patients not receiving concomitant preventive medications			
Patients evaluated — no. (%)	298 (79)	290 (77)	294 (79)
Least-squares mean change from baseline during 12-wk period after first dose	−4.6±0.3	−4.8±0.3	−2.6±0.3
Difference vs. placebo	−1.9±0.4	−2.2±0.4	—
HIT-6 score			
Least-squares mean change from baseline during 4-wk period after last dose‡	−6.4±0.5	−6.8±0.4	−4.5±0.5
Difference vs. placebo	−1.9±0.5	−2.4±0.5	—

* Plus–minus values are least-squares means ±SE. Efficacy analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of a trial regimen and had at least 10 days of postbaseline efficacy assessments regarding the primary end point. To control the type I statistical error rate at 0.05, a preplanned hierarchical testing procedure was applied; end points are presented in the sequence in which they were evaluated. Baseline refers to the 28-day preintervention period unless otherwise indicated.

† P<0.001 for all differences versus placebo, and for the comparison with placebo with respect to the percentage of patients with a reduction of at least 50% in the average number of headache days per month.

‡ Shown is the change from baseline (day 0) during the 4-week period after administration of the last (third) dose of the trial regimen.

group (Table 3). Injection-site induration and erythema were more frequent with fremanezumab than with placebo.

Serious adverse events occurred in 2% of the patients given placebo, 1% of those given fremanezumab monthly, and less than 1% of those given fremanezumab quarterly (Table 3, and Table S2 in the Supplementary Appendix). No serious adverse event occurred in more than one patient. One death occurred in the fremanezumab-quarterly group, 69 days after the patient received fremanezumab at a dose of 675 mg, which was determined on the basis of an autopsy to be due to chronic obstructive pulmonary disease (COPD). Except for the event of fatal COPD, all serious adverse events resolved or were resolving by the end of the trial. One serious adverse event led to discontinuation of the trial; an event of suicidal ideation (assessed by the investigator as being moderate in severity and unrelated to the trial regimen) was reported in a patient in the fremanezumab-monthly group who had a history of depression.

Events of possible trial-agent–induced liver in-

jury (aspartate aminotransferase or alanine transaminase level ≥3 times the upper limit of the normal range, total bilirubin level ≥2 times the upper limit of the normal range, or international normalized ratio >1.5) occurred in three patients in the placebo group (<1%) and five patients in each of the fremanezumab groups (1%) (P=0.73 for each fremanezumab group vs. placebo and P=0.56 for the combined fremanezumab groups vs. placebo) (Table 3). Eight patients (1%) who received fremanezumab had liver enzyme levels that were higher than normal but less than 3 to 5 times the upper limit of the normal range, which were transient and reverted to normal levels without discontinuation of the trial regimen. None of these events were considered by investigators as being serious, and none led to discontinuation of the trial. All the patients with liver enzyme levels that were higher than normal but less than 3 to 5 times the upper limit of the normal range (in the placebo or fremanezumab groups) had used nonsteroidal antiinflammatory drugs or acetaminophen frequently or had used antidepressants daily. Two patients receiving fremanezumab (<1%) had an aspartate aminotransferase or alanine transaminase level more than 5 times the upper limit of the normal range. One of these patients had an alanine transaminase level 6.5 times the upper limit of the normal range at a single visit, and the level normalized without intervention while the patient was receiving the trial regimen. The other patient had an alanine transaminase level 6 times the upper limit of the normal range at baseline as well as an elevated level at visit 4, while being treated for an upper respiratory tract infection with medications containing ethanol. Values normalized after discontinuation of the ethanol-containing drug, while the patient was still receiving the trial regimen.

No participants had anaphylaxis or a severe hypersensitivity reaction. Antidrug antibodies developed in two patients who received fremanezumab quarterly. No clinically significant changes in vital signs, physical-examination findings, or electrocardiographic results occurred in any of the trial groups.

DISCUSSION

This phase 3 trial of fremanezumab in chronic migraine showed a significant benefit of fremanezumab over placebo with respect to the aver-

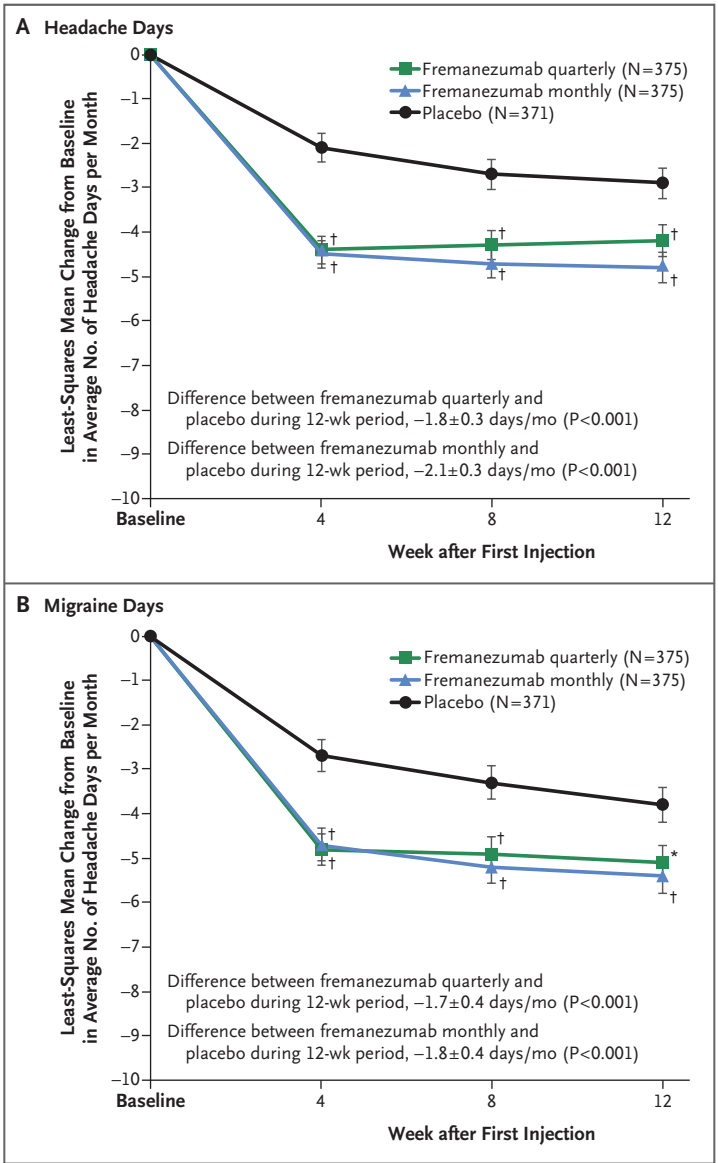

Figure 1. Primary and Secondary End Points.

Panel A shows the change from baseline in the average number of headache days per month during the 12-week period after the first dose of the trial regimen (primary end point), and Panel B shows the change from baseline in the average number of migraine days per month during the 12-week period after the first dose of the trial regimen (secondary end point). A headache day was defined as a calendar day in which headache pain lasted at least 4 consecutive hours and had a peak severity of at least a moderate level, or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any severity or duration. A migraine day was defined as a calendar day in which headache pain lasted at least 4 consecutive hours and met criteria for migraine (with or without aura) or probable migraine (subtype in which only one migraine criterion is absent), or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any duration. An asterisk denotes P=0.006 for the comparison with placebo, and a dagger P<0.001 for the comparison with placebo. I bars indicate standard errors. Changes from baseline to weeks 4, 8, and 12 are part of exploratory analyses.

Table 3. Adverse Events in the Safety Population, According to Trial Group.*

Event	Fremanezumab Quarterly (N=376)	Fremanezumab Monthly (N=379)	Placebo (N=375)
	number of patients (percent)		
At least one adverse event	265 (70)	270 (71)	240 (64)
At least one adverse event related to the trial regimen	186 (49)	194 (51)	159 (42)
At least one serious adverse event	3 (<1)	5 (1)	6 (2)
Any adverse event leading to discontinuation of the trial†	5 (1)	7 (2)	8 (2)
Death‡	1 (<1)	0	0
Adverse events reported in >2% of patients in any group			
Injection-site reactions			
Pain	114 (30)	99 (26)	104 (28)
Induration	74 (20)	90 (24)	68 (18)
Erythema	80 (21)	75 (20)	60 (16)
Hemorrhage	7 (2)	8 (2)	10 (3)
Infections			
Nasopharyngitis	19 (5)	15 (4)	20 (5)
Upper respiratory tract infection	18 (5)	16 (4)	15 (4)
Sinusitis	10 (3)	4 (1)	10 (3)
Dizziness	9 (2)	11 (3)	5 (1)
Nausea	4 (1)	6 (2)	11 (3)
Possible trial-agent–induced liver injury§	5 (1)	5 (1)	3 (<1)
Alanine aminotransferase ≥3× ULN	2 (<1)	3 (<1)	1 (<1)¶
Aspartate aminotransferase ≥3× ULN	3 (<1)	2 (<1)	0
Total bilirubin ≥2× ULN	2 (<1)	0	0
International normalized ratio >1.5	0	0	1 (<1)

* Shown are data collected during the double-blind, placebo-controlled intervention period. The safety population included all the patients who underwent randomization and received at least one dose of a trial regimen. ULN denotes upper limit of the normal range.

† One serious adverse event led to discontinuation of the trial; an event of suicidal ideation (assessed by the investigator as being moderate in severity and unrelated to the trial regimen) was reported in a patient in the fremanezumab-monthly group who had a history of depression.

‡ One death occurred in the fremanezumab-quarterly group as a result of chronic obstructive pulmonary disease; this was determined by the investigator and sponsor to be unrelated to the trial regimen.

§ Patients could have more than one type of possible trial-agent–induced liver injury.

¶ An event was reported in one additional patient but was inadvertently omitted as an adverse event of special interest.

age number of headache days per month (difference vs. placebo, approximately –2 days per month), the number of migraine days, and headache-related disability. Treatment effects were seen within 4 weeks after the initial dose.

These results are consistent with those of the phase 2b trial of fremanezumab in chronic migraine,[14,16] with early onset of efficacy and similar treatment effects for both the monthly and quarterly regimens, although no direct comparison between dose regimens was made. The primary end point as defined in this trial adhered to International Headache Society recommendations and is identical to that used in the pivotal trials of onabotulinumtoxinA,[17-19] a preventive therapy approved by the Food and Drug Administration for chronic migraine. Fremanezumab probably exerts clinical effects through inhibition of the migraine-specific target CGRP and, as a monoclonal antibody, has pharmacologic properties

that are distinct from those of other preventive treatments, including a half-life that supports a long duration of action and long intervals between doses.[20]

Discontinuation of the trial due to adverse events was infrequent, a finding consistent with those of previous trials.[14] Fremanezumab was associated with a higher incidence of injection-site reactions than placebo, but the severity of such reactions did not differ significantly among the trial groups. Because systematic assessment of injection sites was required for 1 hour after dose administration, the rates of the specific injection-site reactions in this trial may have been higher than those previously reported. Fremanezumab, a monoclonal antibody, is not metabolized in the liver and is eliminated through catabolism to smaller peptides or amino acids.[20] Mild transient elevations in liver enzyme levels occurred, and the levels reverted to normal without discontinuation of the trial regimen. All the patients who had these elevations used concomitant medications with a potential to cause increases in liver enzyme levels. Endogenous CGRP is a vasodilator, but there were no hemodynamic changes with fremanezumab. There was one death from chronic pulmonary disease and one case of suicidal ideation in patients receiving the active drug. The latter occurred in a patient with a history of depression and was judged not to be related to the trial drug.

The current trial was conducted in parallel with a trial evaluating fremanezumab in episodic migraine, allowing persons who were ineligible for one trial to be considered for the other. Although the current trial included patients with a long history of disease and those who had previously not had a response to or were currently taking preventive medications, it did not include patients with more refractory disease — those who had not had a response to at least two clusters of preventive medications or who had continuous headache. As in other clinical trials of migraine treatment, eligibility was still restricted to relatively healthy patients. Further studies will be needed to assess the safety and efficacy of fremanezumab in a population of patients with migraine and coexistent diseases. Although the ongoing extension of this trial will provide further insights on efficacy and necessary safety follow-up data, results are not yet available to assess the long-term effects of fremanezumab on safety.

This trial showed that fremanezumab, given monthly or quarterly as subcutaneous injections, was effective for the preventive treatment of chronic migraine.

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